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TITLE: Analytical and Characterization Studies of Organic Chemicals, Drugs and Drug Formulation

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During the annual contract period, 1 July 1997 to 30 June 1998, 9 samples of bulk drugs and dosage formulations were analyzed for identity, purity or potency; 3 special plasma extraction methods were developed, and 13 samples were studied for stability and solubility. Six chiral separation methods were developed and validated. Over two hundred PDF documents were prepared for the WRAIR's online chemical database. One manuscript was submitted for publication.

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FOREWORD

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Peter Lee

PI - Signature June 1998

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INTRODUCTION

This annual report for Contract DAMD17-97-C-7052 covers the period from 1 July 1997 to 30 June 1998. The report consists of a listing of the compounds/samples analyzed and a summary of the number of the types of studies performed. The report also includes a listing of personnel receiving pay from this effort and a bibliography of all publications and meeting abstracts that resulted from this contract.

This contract is concerned with the analytical, characterization, and stability studies of chemicals, drugs, and drug formulations. The work is monitored by Mr. William Y. Ellis, the Contracting Officer Representative (COR), Chief, Chemical Handling and Data Analysis Branch, Division of Experimental Therapeutics, Walter Reed Army Institute of Research (WRAIR).

The overall objective of this project, a continuation of one that started in 1966, is the operation of an analytical laboratory to determine the identity, purity, strength, quality, physical and chemical properties, and stability of bulk pharmaceutical substances and formulated drug products of interest to the USAMRMC Drug Development Program for parasitic and infectious diseases, chemical and biological defense, anti-viral studies, etc. Specific objectives are to: design, develop, validate, and execute methods to determine the following characteristics of candidate bulk pharmaceutical substances and formulated drugs:

- Identity, purity, and strength.
- Stability.
- Other physical and chemical characteristics, including weight variation, content uniformity, and other such compendial requirements.
- Qualitative and quantitative identity of impurities.
- Special projects not covered by the above headings.

ANNUAL REPORT (1997-1998)

Sample Analyses

During the contract period, 1 July 1997 to 30 June 1998, analyses of the following samples were completed and the reports sent to the COR.

1. WR6026; BN42485, 6-methoxy-8-(6-diethylaminohexylamino) lepidine dihydrochloride, 5-mg capsule HPLC assay, Report No. 941.
2. WR6026; BN42494, 6-methoxy-8-(6-diethylaminohexylamino) lepidine dihydrochloride, 15-mg capsule HPLC assay, Report No. 942.
3. WR6026; BN42501, 6-methoxy-8-(6-diethylaminohexylamino) lepidine dihydrochloride, 30-mg capsule HPLC assay, Report No. 943.
4. WR238605; BM08200, N^4-(2,6-dimethoxy-4-methyl-5-(3-(trifluoro-methyl)phenoxy)-8-quinolinyl)-1,4-pentanediamine succinate, 5-mg capsule assay, Report No. 944.
5. WR238605; BM08219, N^4-(2,6-dimethoxy-4-methyl-5-(3-(trifluoro-methyl)phenoxy)-8-quinolinyl)-1,4-pentanediamine succinate, 15-mg capsule assay, Report No. 945.
6. WR243251 and WR243246, qualitative HPLC method to separate WR243251 from WR243246, Report No. 958.
7. WR279396; BN85622, paromomycin and gentamicin in cream formulation; assay for paromomycin, Report No. 938.
8. WR279396; BN85622, paromomycin and gentamicin in cream formulation, assay for gentamicin, Report No. 939.
9. WR279396; BN85622, placebo cream formulation, assay for presence of paromomycin or gentamicin, Report No. 940.

Special Method Developments

Drug blood plasma extraction studies were performed and the following HPLC methods were developed:

1. WR2976; AW23860, extraction and quantitation in rabbit plasma, Report No. 961.

2. WR142490; BE10189, enantioselective HPLC analysis of WR142490 in rabbit plasma, Report No. 960.

3. WR171669; BL56676 and WR178460; BN78716, extraction of WR171669, (±)-Halofantrine and WR178460, (±)-Desbutylhalofantrine from rabbit plasma; subsequent quantitation by chiral HPLC, Report No. 962.

Stability and Solubility Studies

Stability and solubility studies on the following samples have been completed and the reports submitted to the COR.

1. WR171669AS; BL56676, 1,3-dichloro-6-trifluoromethyl-9-[1-hydroxy-3-(di-n-butylamino)propyl]phenanthrene hydrochloride, 9-yr shelf-life stability study, Report No. 957.

2. WR178460; BN78716, lot JEF-28030-36, desbutylhalofantrine hydrochloride, room-temp, 1.5-yr shelf-life stability, Report No. 966.

3. WR178460; BN78716, desbutylhalofantrine, 1-yr room-temperature shelf-life stability study, Report No. 952.

4. WR178460; BN78716, desbutylhalofantrine, 35 °C 3-mo accelerated stability study, Report No. 946.

5. WR178460; BN78716, desbutylhalofantrine, 50 °C 3-mo accelerated stability study, Report No. 947.

6. WR178460; BN78716, desbutylhalofantrine, 35 °C 9-mo accelerated stability study, Report No. 963.

7. WR178460; BN78716, desbutylhalofantrine, 50 °C 9-mo accelerated stability study, Report No. 964.

8. WR242511AE; BM05816, 8-[(4-amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL-tartrate, 7-yr shelf-life stability study, Report No. 956.

9. WR243251AB; BJ45753, 7-Chloro-3-(2",4"-dichlorophenyl)-1-[[3'-(dimethylamino)propyl]imino]-1,2,3,4-tetrahydro-9-(10H)-acridone, 9-mo shelf-life stability study, Report No. 953.

10. WR250547AB; BL34170, 9-mo shelf-life stability study, Report No. 954.

11. WR250548AB; BL29759, 9-mo shelf-life stability study, Report No. 955.

12. WR255663AK; BM04131, 8-yr shelf-life, Report No. 965.

13. WR255663AK; BM04131, thermal and shock stability, Report No. 949.

Chiral Separations and Method Validations

Chiral separations on the following samples have been completed and the reports have been sent to the project COR.

1. WR178460; BN78716, desbutylhalofantrine hydrochloride, chiral HPLC assay validation, Report No. 918.

2. WR242511; 8-[(4-amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL-tartrate, a method development and validation of a chiral HPLC method for racemic bulk, Report No. 948.

3. WR280510; BN65139, R(-)- 8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL-Tartrate, validation of a chiral HPLC method, Report No. 950.

4. WR280511; BN65148, S(+)-8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL-Tartrate, validation of a chiral HPLC method, Report No. 951.

5. WR280691; BN79803, (-) desbutylhalofantrine hydrochloride, chiral HPLC validation, Report No. 936.

6. WR280823; BN78716, (+) desbutylhalofantrine hydrochloride, chiral HPLC validation, Report No. 937.

Portable Document Format (PDF) Reports

A large number (205) of completed technical reports in electronic portable document format (PDF) were uploaded to WRAIR's ETIMAGE server. These PDF documents were:

sri758.pdf, sri759.pdf, sri761.pdf, sri762.pdf, sri763.pdf, sri764.pdf, sri765.pdf, sri766.pdf, sri767.pdf, sri768.pdf, sri769.pdf, sri770.pdf, sri771.pdf, sri772.pdf, sri773.pdf, sri774.pdf, sri775.pdf, sri776.pdf, sri777.pdf, sri778.pdf, sri779.pdf, sri780.pdf, sri781.pdf, sri782.pdf, sri783.pdf, sri784.pdf, sri785.pdf, sri786.pdf, sri787.pdf, sri788.pdf, sri789.pdf, sri790.pdf, sri791.pdf, sri792.pdf, sri793.pdf, sri794.pdf, sri795.pdf, sri796.pdf, sri797.pdf, sri798.pdf, sri799.pdf, sri800.pdf, sri801.pdf, sri802.pdf, sri803.pdf, sri804.pdf, sri805.pdf, sri806.pdf, sri807.pdf, sri808.pdf, sri809.pdf, sri810.pdf, sri811.pdf, sri812.pdf, sri813.pdf, sri814.pdf, sri815.pdf, sri816.pdf, sri817.pdf, sri818.pdf, sri819.pdf, sri820.pdf, sri821.pdf, sri822.pdf, sri823.pdf, sri824.pdf, sri825.pdf, sri826.pdf, sri827.pdf, sri828.pdf, sri829.pdf, sri830.pdf, sri831.pdf, sri832.pdf, sri833.pdf, sri834.pdf, sri835.pdf, sri836.pdf, sri837.pdf, sri838.pdf, sri839.pdf, sri840.pdf, sri841.pdf, sri842.pdf, sri843.pdf, sri844.pdf, sri845.pdf, sri846.pdf, sri847.pdf, sri848.pdf, sri849.pdf, sri850.pdf, sri851.pdf, sri852.pdf, sri853.pdf, sri854.pdf, sri856.pdf, sri857.pdf, sri858.pdf, sri859.pdf, sri860.pdf, sri861.pdf, sri862.pdf, sri863.pdf, sri864.pdf, sri865.pdf, sri866.pdf, sri867.pdf, sri868.pdf, sri869.pdf, sri870.pdf, sri871.pdf, sri872.pdf, sri873.pdf, sri874.pdf, sri875.pdf, sri876.pdf, sri877.pdf, sri878.pdf, sri879.pdf,

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Publications

The following manuscript has been submitted for publication:

1. "A Chiral HPLC Analysis of a Substituted Aminoquinoline Analog, WR242511", by Lori L. Olson, Tina Nguyen, John Pick, and William Y. Ellis, was submitted for potential publication.

Abstract: This paper reports, for the first time, a simple and sensitive chiral HPLC-based method for the enantiomeric resolution and quantitation of a racemic aminoquinoline analog, WR242511, a drug of interest in the treatment of Malaria, pneumocystis pneumonia and cyanide prophylaxis. Baseline resolution of the racemate into its enantiomers was achieved by utilizing a polysaccharide-type HPLC column. Validation data for precision, linearity, accuracy, lower limit of detection and stability of each enantiomer and the racemate are presented. This method may be applicable to separate other racemic aminoquinoline analogs, and with modification, could be considered for scaled up production of the enantiomers.

Personnel

A listing of personnel who received major contract support is as follows:

Peter Lim, P.I.
Lori Olson, Assistant P.I.
John Pick, Chemist
Tina Nguyen, Chemist

Summary/Conclusion

During the annual contract period, 9 samples of bulk drugs and dosage formulations were analyzed for identity, purity or potency, 3 special plasma extraction methods were developed, and 13 samples were studied for stability and solubility. Six chiral separation methods were developed and validated. Over two hundred PDF documents were prepared for the WRAIR's online chemical database. One manuscript was submitted for publication.

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